Review Article

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Management Strategies for Potassium Levels During Non-steroidal Mineralocorticoid Receptor Antagonist Therapy: A Comprehensive Review

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Diabetic kidney disease (DKD) is a leading cause of chronic kidney disease (CKD). Recent advancements highlight the role of finerenone, a non-steroidal mineralocorticoid receptor antagonist (nsMRA), in DKD management. Studies like FIDELIO-DKD, FIGARO-DKD, and FIDELITY have demonstrated finerenone's efficacy in reducing CKD progression and cardiovascular risks in DKD patients. Trials reveal higher incidence of hyperkalemia in finerenone groups compared to controls. Asian populations are noted to have a higher risk, emphasizing the need for close monitoring. To manage hyperkalemia, evidence-based protocols suggested starting finerenone with potassium level below 4.8 mEq/L, discontinuing if potassium level exceed 5.5 mEq/L. Strategies include dietary potassium restriction, potassium binders, and frequent monitoring. While these managements help mitigate risks, real-word challenges call for further evidence to refine practical guidelines. Finerenone emerges as a promising therapy for DKD but requires careful management to prevent hyperkalemia, ensuring optimal patient outcomes.

Key Words: Dabetic kidney disease, Non-steroidal mineralocorticoid receptor antagonists, Finerenone, Hyperkalemia

INTRODUCTION

Principles of pharmacological treatment for diabetic kidney disease

Diabetic kidney disease (DKD) affects nearly 25.4% of adult patients with diabetes mellitus, according to a recent factsheet released in South Korea[1]. Globally, diabetes mellitus (DM) is well known as the most common cause of progressive chronic kidney disease (CKD). As the average age of patients with diabetes increases, the incidence of DKD is also expected to increase[2]. Currently, DKD refers not only to diabetic nephropathy but also to CKD with diabetes[3]. It has classically been known that DKD results from hyperfiltration of nephrons and hypertrophy of nephrons, leading to nephron loss and fibrosis via metabolic and inflammatory process[4]. In terms of hemodynamics, tubuloglomerular feedback triggered by reduced sodium delivery to the macula densa in DKD leads to glomerular hyperfiltration[5]. The renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the progression of DKD. In DKD, RAAS activation causes hemodynamic changes, glomerular hyperfiltration, endothelial-mesenchymal transition, and renal fibrosis.

Recent evidence suggests that finerenone may be effective in treating DKD with microalbuminuria. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) help suppress RAAS hyperactivation[6-8]. After

Table 1. Serum potassium levels in previous studies related to finerenone

Trial	Definition of hyperkalemia	Incidence of hyperkalemia	
		Placebo	Finerenone
FIDELIO-DKD	>5.5 mmol/L	9.0%	18.3%
FIGARO-DKD	>5.5 mmol/L	5.3%	10.8%
FIDELITY	>5.5 mmol/L	5.9%	12.0%
FIDELIO-Asian	>5.5 mmol/L	17.0% (Non-Asian group: 6.6%)	26.0% (Non-Asian group: 15.9%)

the use of medications such as SGLT2 inhibitors and GLP1 agonists in DKD, finerenone has emerged as a novel treatment for DKD and heart failure[9-11]. Finerenone is a non-steroidal mineralocorticoid receptor antagonist with higher sensitivity and selectivity compared to steroidal mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone[12]. Studies on the efficacy of spironolactone and eplerenone demonstrated the effect of reducing blood pressure and proteinuria, however, failed to reveal reno-protective effect because of the development of acute kidney injury and/or hyperkalemia[13]. Due to its bulky structure and independent mechanism of action, finerenone has a 500-fold higher specificity compared to other steroidal MRAs, with fewer side effects, such as gynecomastia.

Pivotal studies on finerenone

Three key trials—FIDELIO-DKD[14], FIGARO-DKD[15], and FIDELITY[16]—reported improved renal and cardiovascular outcomes in DKD patients with microalbuminuria. All participants received maximum tolerable renin-angiotensin system blockade in these trials. The FIDELIO-DKD trial included 5,734 patients with type 2 diabetes and CKD characterized by reduced kidney function (eGFR between 25 to 60 ml/min/1.73m^2) with microalbuminuria (UACR ≥300 and <5,000 mg/g), and followed up for 2.7 years. The FIGARO-DKD trial involved 7,437 participants whose eGFR between 25 to 90 ml/min/1.73m^2) with microalbuminuria (UACR ≥30 to <300 mg/g), or albuminuria between 300 to 5,000 mg/g with an eGFR over 60 ml/min/1.73 m^2), and followed up for 3.4 years. The FIDELIO-DKD, the FIGARO-DKD, and the pooled FIDELITY trial showed improved cardiovascular outcome and reduced CKD progression. Pooling data from both trials (over 13,000 patients) showed a 14% reduction in the composite cardiovascular outcome and a 23% reduction of CKD progression.

Hyperkalemia in finerenone

Hyperkalemia is a common complication in DKD patients, particularly in those with progressive kidney disease[17,18]. Aldosterone plays a crucial role in potassium homeostasis by regulating renal outer medullary potassium channel in the kidney collecting duct[15]. When aldosterone acts in the kidneys, sodium reabsorption and potassium secretion are accelerated in the collecting ducts. In the hyperglycemic state, the RAAS is activated, leading to hyperfiltration, inflammation, and fibrosis in the kidneys of diabetes patients. To slow the progression of chronic kidney dysfunction, ACE inhibitors, ARBs, and finerenone suppress the RAAS. However, due to their pharmacological effects, MRAs can cause hyperkalemia[19]. For instance, the incidence of hyperkalemia was higher in the finerenone group in three large trials: FIDELIO-DKD, FIGARO-DKD, and FIDELITY (Table 1)[14-16]. In these trials, participants with serum potassium levels of 4.8 mEq/L or higher were excluded at baseline. Although there were no differences in severe hyperkalemia, 18.3% of participants taking finerenone developed hyperkalemia compared to 9.0% of those not taking finerenone in the FIDELIO-DKD trial. In the FIGARO-DKD trial, which included patients with better kidney function, the incidence of hyperkalemia was 10.8% in the finerenone group and 5.3% in the control group. The FIDELITY trial showed similar results regarding the development of hyperkalemia.

Ways to manage hyperkalemia

Unified guidelines for managing hyperkalemia are scarce,

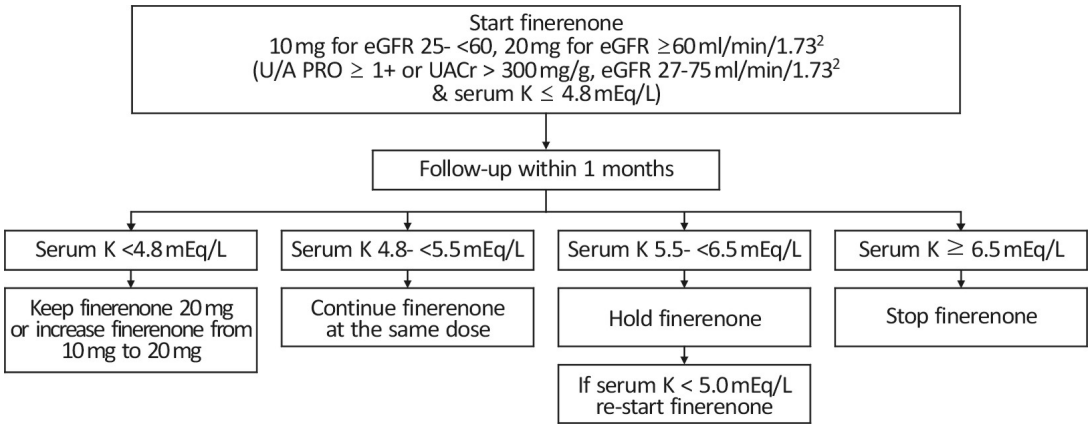

Fig. 1. Flowchart for hyperkalemia management when prescribing finerenone.

partly due to the varying definitions of the condition. In heart failure, intervention is recommended when serum potassium exceeds 5.0 mEq/L[20], which is stricter than that recommended in kidney disease. According to the KDIGO guidelines[21], the FIDELIO-DKD and FIGARO-DKD trials defined hyperkalemia as a serum potassium level above 5.5 mEq/L, with severe hyperkalemia considered as levels over 6.5 mEq/L, associated with serious complications such as arrhythmia. Furthermore, a post-hoc analysis of the FIDELIO-DKD trial showed higher rates of hyperkalemia-related adverse events in Asian patients compared to non-Asian patients[22], giving caution to preventing hyperkalemia in Asian groups. Hyperkalemia can be influenced by several factors, including underlying comorbidities, age, food intake, and medications. Identifying factors that contribute to increased serum potassium in individual patients and ensuring close follow-up are practical strategies. It would be rational to follow protocols whose results have been validated by previous studies. In a post-hoc analysis from the FIDELIO-DKD trial[23], the authors suggested that close monitoring and management strategies for hyperkalemia would minimize its impact on patients' outcomes. Based on large studies with finerenone[14-16], it is recommended to initiate finerenone treatment when the serum potassium level is less than 4.8 mEq/L, with follow-up at 1 and 4 months (± 7 days). Finerenone should be discontinued if potassium exceeds 5.5 mEq/L, alongside other strategies to manage hyperkalemia (Fig. 1). Methods to control hyperkalemia include reducing dietary potassium intake and using medications such as potassium binders, with or without finerenone. Serum potassium levels should be monitored repeatedly within 72 hours after discontinuing finerenone. However, certain aspects of these protocols, such as the follow-up duration, may be challenging to implement in real-world clinical settings. Further evidence is needed to establish practical and comprehensive guidelines for the use of finerenone.

CONCLUSIONS

Finerenone is a novel agent for treating DKD and potentially heart failure. However, caution is required when prescribing it to patients with hyperkalemia. Therefore, hyperkalemia should be managed and prevented before starting finerenone.

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